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T-cell vaccination in multiple sclerosis: update on clinical application and mode of action

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). Autoreactive T cells specific for myelin antigens are considered to play a prominent role in the initiation of the local inflammatory response, ultimately leading to myelin damage. Several studies indicate that autoreactive T cells are not completely deleted in the thymus, but are part of the normal T cell repertoire. Accidentally activated autoreactive T cells, however, may not automatically lead to autoimmune disease. Several reports support the existence of peripheral regulatory networks that prevent the activation and expansion of pathogenic T cells. Anti-idiotypic and anti-ergotypic T cells are part of this regulatory network and are thought to control autoreactive T cells by recognition of certain clonotypic and ergotypic determinants. These clonotypic networks may not function properly in patients with MS. Immunization with attenuated autoreactive T cells, termed T cell vaccination (TCV), may enhance or restore the regulatory networks to specifically suppress the autoreactive T cells as shown in experimental autoimmune encephalomyelitis (EAE), a commonly used animal model for MS. In the past decade, TCV has been tested for MS in several clinical trails. This review summarizes these clinical trails and updates our current knowledge on the mode of action of T cell vaccination.

Keywords: Autoreactive T cells; T cell vaccination; Regulatory networks; Anti-clonotypic T cells; Anti-ergotypic T cells

1. Introduction: the concept of T-cell vaccination

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by focal areas of demyelination in the CNS [1]. Autoimmune processes involving myelin reactive T cells are considered to play an essential role in the pathogenesis of MS (reviewed by Hellings et al. [2]). In vivo activated myelin basic protein (MBP) reactive T cells are clonally expanded in blood of MS patients, and may persist for many years in some patients [3,4]. The activation of MBP reactive T cells via molecular mimicry could be a common process, as suggested by the high level of cross-reactivity of MBP reactive T cells to various microbial ligands, even in the absence of any sequence homology [5,6]. Accidentally stimulated autoreactive

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T cells, however, may not automatically lead to autoimmunity. Indeed, several observations support the existence of a peripheral regulatory network that prevents activation or expansion of pathogenic T cells [7]. An imbalanced regulatory network may lead to suboptimal suppression of activated pathogenic T cells and give rise to autoimmunity. Administration of attenuated autoreactive T cells as a vaccine, 'T cell vaccination', enhances regulatory networks to specifically suppress the eliciting autoreactive T cells as shown in experimental autoimmune encephalomyelitis (EAE), an animal model of MS [8,9].

The concept of T cell vaccination (TCV) is, at least partially, analogous to classical vaccination against infectious disease. However, the agents to be eliminated or neutralized are not foreign microbial agents but a pathogenic autoreactive T cell population. Initial experiments in rats demonstrated that immunization with attenuated encephalitogenic T cells protects naive animals from a subsequent induction of EAE and induces remission of the disease [8]. TCV induces regulatory networks that specifically suppress vaccine T cells by activating T cells specific for a clonotype-specific determinant ('anti-idiotypic response') [9]. Furthermore, after immunization with attenuated recently activated T cells, 'anti-ergotypic responses' were demonstrated by regulatory T cells that recognize activation markers on the vaccine cells [10].

2. Clinical trials

Based on the results of successful treatment of TCV in animal models, our group conducted a pilot trial in a small number of MS patients. Eight patients with relapsing–remitting or chronic progressive MS were immunized three times with activated and subsequently irradiated autologous MBP-specific T cell clones at intervals of 2–4 months [11–13]. This study demonstrated that subcutaneous inoculations of autologous vaccine clones are well-tolerated and cause no adverse effects. Clinical data suggested a moderate clinical improvement in five out of eight MS patients with respect to reduced rate of exacerbations, stabilization of EDSS scores and MRI data on brain lesions [11]. Administration of the vaccines induced an anti-idiotypic T cell response, specifically recognizing the vaccine clones, accompanied with a progressive depletion of circulating MBP-reactive T cells in all patients [13,14]. A long-term follow-up study revealed that in most of the patients MBP-reactive T cells remained undetectable for 1–2 years after vaccination. After an additional period of 1–3 years, MBP-reactive T cells reappeared in five MS patients, which coincided with clinical relapses in two patients. The isolated T cell clones possessed similar functional properties, but had a different clonal origin as compared to MBP-reactive T cells identified prior to vaccination. In subsequent rounds of TCV, these reappearing T cell clones could again effectively be depleted [15]. More recently, 49 MS patients were treated in an extended open label phase I trial to study safety, clinical effects and cellular and humoral immune responses in a larger group of patients [16]. Zhang and co-workers carried out similar extended preliminary clinical trials using an identical protocol in 54 MS patients (28 RR-MS, 26 SP-MS). These studies confirmed that vaccination with MBP-reactive T cells induces immune responses [17], resulting in the depletion or suppression of circulating MBP-reactive T cells. Clinical results indicated that these enhanced immune responses coincided with a prolonged time to progression in both RR- and SP-MS patients as compared with the natural history of MS. Correale, Weiner and co-workers performed a TCV pilot trial using bovine myelin-reactive T cell lines as vaccines in four SP-MS patients [18]. Immunological data showed a progressive decline of circulating whole myelin-reactive T cells. After vaccination, cytotoxic T cells recognizing the inoculates were isolated from the peripheral blood of two MS patients. Although these preliminary clinical trials provided important clinical indications, the treatment efficacy must be evaluated in double-blind placebo-controlled clinical trials. Currently, there are phase I and II trials ongoing or planned in Diepenbeek, Houston, Los Angeles, Jerusalem and Buenos Aires using different vaccination protocols (Table 1). These studies will provide further insight into the boosted regulatory mechanisms, and subsequent therapeutic effects, and may provide infor-

Table 1
Overview of human T cell vaccination trials*

Immune disease	Vaccine composition	Subjects	Clinical phase	Center
Multiple sclerosis	Blood derived T-cell lines specific for:			
	MBP	RR-MS ($n=5$) PP-MS ($n=1$) SP-MS ($n=2$)	I (Completed) [11]	LUC, Diepenbeek, Belgium
		RR-MS ($n=49$)	I (Completed) [16]	LUC, Diepenbeek, Belgium
	MBP peptides	RR-MS ($n=28$) SP-MS ($n=26$)	II (Completed) [17]	Baylor College, Houston, USA
	Whole bovine myelin	SP-MS ($n=4$) SP-MS ($n=80$)	I (Completed) [18] II (Ongoing)	USC, Los Angeles, USA
	Hydrolyzed bovine brain white matter	CP-MS ($n=40$)	I (Ongoing)	Buenos Aires, Argentinia
	Myelin peptides	RR-MS ($n=30$)	I/II (Ongoing)	Hadassah Hospital, Jerusalem, Israel
	MBP and MOG peptides	RR-MS ($n=20$)	I/II (Ongoing)	Sheba Medical Center, Jerusalem, Israel
	CSF-derived T cells	PP-MS ($n=4$)	I (Completed) [44]	Harvard Medical School, Boston, USA
	CSF-derived activated $CD4^+$ T cells	RR-MS ($n=4$) SP-MS ($n=1$)	I (Completed) [28]	LUC, Diepenbeek, Belgium
	CSF-derived activated $CD4^+$ T cells	RR-MS ($n=60$)	II (Ongoing)	LUC, Diepenbeek, Belgium
Rheumatoid Arthritis	Synovial tissue/fluid derived T-cells	RA ($n=13$)	I (Completed) [24]	University Hospital, Leiden, The Netherlands
Crohn's Disease	Gut-derived $CD4^+$ T-cells	CD ($n=2$)	Pilot [26]	University of Aarhus, Denmark
AIDS	Blood derived T cells specific for rCD4	HIV ($n=7$)	I (Completed)	Hadassah Hospital, Jerusalem, Israel

* Based on published data and website www.t-cellvaccination.org.

mation on the most appropriate protocol for T cell vaccination. Whether T cell vaccination should also be considered for other T-cell mediated (auto)immune diseases remains to be studied. However, TCV has been proven to be effective in several experimental animal models including adjuvant and collagen-induced arthritis, type I diabetes, experimental autoimmune uveitis and even skin graft rejection [19–23]. Meanwhile, pilot trials in small cohorts of patients have been undertaken for rheumatoid arthritis, Crohn's Disease and AIDS [24–26] (Table 1).

3. Vaccine preparation/composition

In most TCV trials the T cell vaccine is composed of blood-derived autologous, activated, clonally expanded $CD4^+$ MBP reactive T cell clones or lines. It is now widely accepted that T cells recognizing myelin components other than MBP may also contribute to the disease process in MS (reviewed in Hellings et al. [2]). Proteolipid protein (PLP) and myelin oligodendrocyt protein (MOG) may also play an important role as candidate myelin antigens in the autoimmune mediated

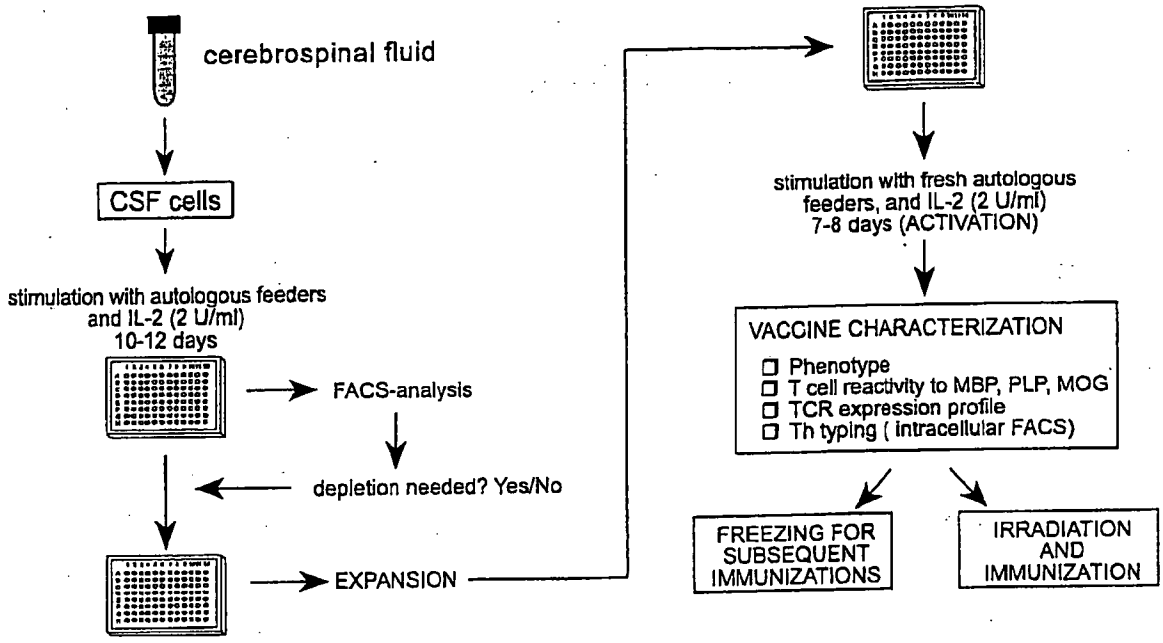

Fig. 1. Schematic overview of current protocol for vaccine preparation.

demyelination. Incorporating T cell populations specific for these autoantigens in the vaccine may improve the effectiveness of the current TCV protocol. However, technically it is almost impossible to generate T cell clones specific for three different myelin antigens with the current protocol design. We, therefore decided to explore the possibility to use IL-2 expanded CD4 T lymphocytes from CSF as vaccine. Activated myelin reactive T cells accumulate in CSF of patients with MS, and low dose IL-2 stimulation can be used to expand these cells from CSF [27]. Moreover, CSF lymphocytes better reflect the repertoire of inflammatory cells infiltrating the parenchyma and they may contain infiltrating pathogenic cells relevant to the disease process because of its proximity to the target organ in MS. To study safety, feasibility and immune effects of TCV, we conducted a pilot clinical trial of TCV with activated $CD4^+$ T cells derived from CSF in five MS patients (4 RR, 1 CP) [28]. CSF lymphocytes were cultured in the presence of rIL-2 and depleted for CD8 cells (Fig. 1). After 5–8 weeks CSF T-cell lines (TCL) were almost pure $TCR\alpha\beta^+CD4^+$ cells of the Th1/Th0 type. The TCL showed reactivity to MBP, MOG and/or PLP as tested by Elispot and had a restricted clonality. Three immunizations with irradiated CSF vaccines (10 million cells) were administered at intervals of 2 months. The vaccinations were well tolerated and no toxicity or adverse effects were reported. Proliferative responses against the CSF vaccine were observed in three to five patients. Anti-ergotypic responses were observed in four to five patients. Anti-MBP/PLP/MOG reactivities remained low or were reduced in all patients. Based on these results, we recently initiated a double-blind placebo-controlled trial with 60 MS patients to study the effects of TCV with CSF-derived vaccines in early RR MS patients.

A possible drawback of the CSF protocol is that the T cell vaccine is not as well characterized as compared to the classical vaccine preparation. Although our data indicate that the CSF cultures have a restricted clonal profile and show reactivity to multiple myelin antigens [28], we cannot exclude the presence of activated $CD4^+$ T cells specific for other antigens. In addition, the CSF cultures used in our protocol are positive for IL-2Rα (CD25), which might mislead one to think that regulatory T cells

(Treg cells) may be present in the cultures. However, while $CD25^+$ Treg cells are highly anergic and have suppressive activity, our cultures showed neither of these characteristics (unpublished results). Other groups also optimized the vaccine composition by including potentially relevant pathogenic T-cell populations (Table 1). One approach taken is the use of whole (bovine) myelin or a mixture of different myelin peptides to generate vaccine T cell lines [18,29]. Other groups have taken an approach comparable to ours by isolating pathogenic T cells from the place closest to the disease site: gut-derived T cells for Crohn's disease or synovial T cells for rheumatoid arthritis [24,26]. Our growing knowledge on the autoreactive T cell subsets potentially involved in the MS pathogenesis will help us to further improve the composition of the T cell vaccines.

4. Mode of action: the complexity of anti-vaccine responses

Although the exact mechanisms by which T cell vaccination ameliorates autoimmune disease in animal models remain unclear, indirect evidence suggests that the anti-vaccine T cell responses specifically target the immunizing T cell clones by recognition of a clonotype specific determinant ('the idiotype'), most likely the T cell receptor (TCR) [9,19]. In addition to these anti-idiotypic T cell responses, other regulatory mechanisms are thought to contribute to the protective immunity induced by T cell vaccination. Cohen and colleagues observed that anti-clonotypic T cells might possibly induce autoreactive T cells to shift from Th1 to Th2 [30]. Lohse et al. further demonstrated that anti-ergotypic T cell responses directed at activation markers ('the ergotope') may partially account for the suppression of activated autoreactive T cells after vaccination [10]. In addition, T cell vaccination in EAE was shown to induce humoral responses that inhibited the proliferation of vaccine cells [31]. Taken together, these findings reveal that TCV in EAE induces a complex immune response that results in the neutralization of pathogenic T cells.

Little is known about the mechanism of T cell vaccination in MS. We have previously described both anti-clonotypic and anti-ergotypic T cell responses to the vaccine clones in vaccinated patients [13,14]. However, it is possible that other cell subsets including B-cells and $\gamma\delta^+$ T cells are involved in the suppression or down regulation of autoreactive T cells after T cell vaccination. In this part we summarize the currently available data on TCV-induced immune responses in MS, thus providing further insight into the mechanism of T cell vaccination (see Fig. 2).

4.1. Anti-idiotypic T-cell responses

Our studies indicated that $CD8^+$ anti-clonotypic T cells isolated from vaccinated MS patients showed cytotoxic and inhibitory activity towards the immunizing MBP reactive T cells in a MHC class I restricted way [13,14]. Anti-clonotypic T cells may recognize TCR determinants within the hypervariable CDR3 (complementarity-determining region 3) region or less variable CDR2 regions, as predicted by characteristic sequence diversity within these regions [14,32,33]. In addition, Vandenbark et al. have demonstrated that $CD4^+$ T cells can be stimulated by TCR peptides presented in the context of MHC class II molecules [34]. The anti-TCR peptide T cells described by these authors produce high levels of IL-10 and may induce bystander suppression of circulating MBP reactive T-cell clones as demonstrated in in vitro experiments [34].

There are several models that explain how the idiotypic determinants of target TCR are presented to and recognized by anti-idiotypic T cells. Endogenous TCR peptides can be presented by self-MHC (I and II) to anti-idiotypic T cells [35,36]. There is experimental evidence indicating that peptides of surface molecules are presented by MHC class I molecules [37]. Accordingly, TCR-peptides could be generated during normal protein turnover of endogenously produced clone specific T cell receptors. Alternatively, TCR proteins could be taken up from degenerating T cells by antigen-presenting cells, such as macrophages, processed and displayed on the macrophage surface in MHC class II-bound form. Both of these presentation pathways may be involved since our data and previous reports suggested that T cell (receptor) vaccination

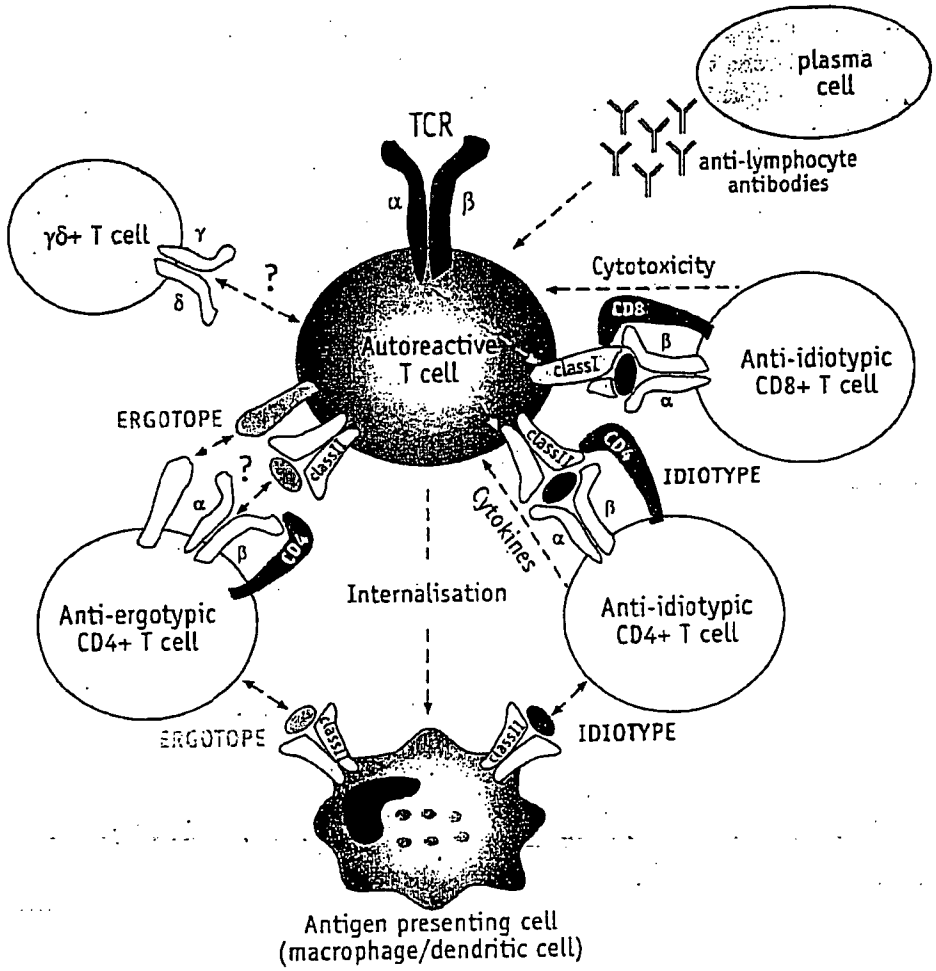

Fig. 2. Complexity of anti-vaccine responses induced by TCV. See text for detailed information on the different components of the anti-vaccine response.

induces both $CD8^+$ MHC class I restricted and $CD4^+$ MHC class II restricted anti-idiotypic T cells [12,34].

4.2. Anti-ergotypic T-cell responses

Anti-ergotypic T cells have also been indicated to be important in TCV-induced immune responses. Anti-ergotypic T cells are less well characterized and react with an unknown marker commonly expressed on the surface of activated T cells [10]. TCV in EAE is only effective when the vaccine cells are activated. Moreover, adoptive transfer of anti-ergotypic T cell lines could downregulate EAE [38]. These findings highlight the involvement of anti-ergotypic responses in the protective effects of TCV. Cytokine receptors including CD25 (IL-2R) and TNFR have been identified as candidate targets of anti-ergotypic T–T interactions [38]. Attempts to characterize anti-ergotypic T cells have been hampered by their poor in vitro growth characteristics. Short-term anti-ergotypic lines isolated from vaccinated MS patients have a mixed phenotype (both $CD4^+$ and $CD8^+$ cells) and recognize activated T cells both via MHC restricted and non-MHC restricted mechanisms. Moreover they were able to secrete IFN-γ, TNF-α but not TGF-β [39]. The exact mode of action, however, remains elusive. Our previous TCV trials demonstrated that TCV induces long-term immune responses in a clonotype specific manner [14]. In addition, we found increasing anti-ergotypic proliferative responses after each round of vaccina-

tion [13,28]. However, this anti-ergotypic response was transient since it declined only a few months after the last vaccination. A further characterization of the cell types involved in these non-specific responses will help us understand their actual role in the mechanisms of TCV.

4.3. Humoral responses

In view of the observations that anti-lymphocyte antibodies play a major role in the protective effects of T cell vaccination in EAE [31], we performed a detailed evaluation of the humoral responses to vaccine cells in patients treated with T cell vaccination. The presence of antibodies was evaluated in serum of vaccinated patients which could either bind to living vaccine cells (by flow-cytometry) or bind to protein extracts made from vaccine clones (by Western blotting). In addition, the effects of serum antibodies on antigen specific proliferation of the vaccine clones were studied. No major antibody responses were observed towards the vaccine clones in vaccinated patients [16]. Although a low level of antibody reactivity against the vaccine was found in one patient, the humoral responses are clearly less important in T cell vaccination as compared to the anti-vaccine antibody responses in EAE. A recent study found more pronounced humoral responses specific for lymphocyte components including TCR epitopes [40]. Further studies need to resolve whether different routes of administration cause the discrepancies between human and animal experiments, and whether the use of adjuvants may increase the antibody responses against the vaccine in patients. However, the successful depletion of autoreactive T cells even in the absence of an efficient antibody response suggests that humoral responses to T cell vaccination may not be necessary to induce protective effects in humans.

4.4. Other lymphocyte subsets

It is possible that other lymphocyte populations also are involved in the suppression or down regulation of autoreactive T cells after T cell vaccination. For instance, we showed that γδ T cells respond to vaccine cells and may thus play a role in the regulation of autoreactive T cells by T cell-T cell interactions or by the secretion of soluble factors [41]. Several vaccinated patients showed an in vivo enrichment of γδ T cells. These γδ T cells reacted to activated T cells and may thus be partly responsible for the above mentioned anti-ergotypic responses. We extended these studies in a group of 49 MS patients to characterize the cellular responses that are induced by T cell vaccination. The phenotypic characteristics of short-term anti-vaccine cultures indicated that $CD4^+$ T cells, $CD8^+$ T cells but also $CD4^-$ $CD8^-$ cells respond to the vaccine [16]. Our data suggest that TCR $\alpha\beta^+$ $CD8^+$ T cells display the most important direct anti-idiotypic effects towards the vaccine clones, while $CD4^+$ T cells are the predominant cytokine producers upon stimulation with the vaccine cells. In addition, several other lymphocyte populations including γδ T cells and NK cells are expanded upon stimulation with the vaccine. Recently, a defective function of regulatory cells -including $CD4CD25^+$ Treg cells and NKT-cells- have been ascribed to be potentially responsible for insufficient controlling of peripheral autoimmune responses [42,43]. Recently, Vandenbark and coworkers indicated that vaccination with TCR-peptides leads to a boosting of anti-TCR T cells that show very similar characteristics to the $CD4CD25^+$ Tregs (personal communications). Whether TCV may be able to restore these regulatory T cell subsets remains to be studied. It is possible that the $CD4CD25^+$ Treg cells take part in the complex anti-vaccine responses mentioned above.

5. Mode of action: concluding remarks

In conclusion, immunization with attenuated autoreactive T cells induces a complex cellular response specifically targeted at the vaccine cells. In addition to the anti-idiotypic and anti-ergotypic T cells, several uncommon lymphocyte populations including γδ T cells and NK cells are also expanded upon stimulation with the vaccine, suggesting that these cells may also play a role in immunoregulatory T–T cell interactions. While our T cell vaccination protocol does not seem to induce major antibody responses, other studies found more pronounced humoral responses. Further studies are necessary to resolve if any of the above mentioned components of the complex anti-vaccine response are sufficient to induce the protective effects seen after TCV. This may in turn lead to the development of more

simplified therapies aimed at specifically boosting one of the specific subsets of cells.

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Take-home messages

- T cell vaccination (TCV) is an experimental immunotherapy for multiple sclerosis in which patients are immunized with attenuated autologous autoreactive T cells.
- T cell vaccination aims at inducing regulatory immune responses to downregulate potentially pathogenic autoreactive T cells.
- Different lymphocyte subsets including $CD4^+$ and $CD8^+$ T cells, B cells and $\gamma\delta^+$ T cells contribute to the complex immune response induced by TCV.
- Clinical trials are ongoing in different centers and will help to further elucidate the mode of action of T cell vaccination and improve the composition of T cell vaccines.
- T cell vaccination may be applicable in a wide range of T cell mediated immune diseases including MS, rheumatoid arthritis, Crohn's disease and graft rejection.

References

[1] Ffrench-Constant C. Pathogenesis of multiple sclerosis. Lancet 1994;343:271–5.
[2] Hellings N, Raus J, Stinissen P. Insights into the immunopathogenesis of multiple sclerosis. Immunol Res 2002;25:27–51.
[3] Hellings N, Gelin G, Medaer R, Bruckers L, Palmers Y, Raus J, et al. Longitudinal study of antimyelin T-cell reactivity in relapsing–remitting multiple sclerosis: association with clinical and MRI activity. J Neuroimmunol 2002;126: 143–60.
[4] Goebels N, Hofstetter H, Schmidt S, Brunner C, Wekerle H, Hohlfeld R. Repertoire dynamics of autoreactive T cells in multiple sclerosis patients and healthy subjects: epitope spreading vs. clonal persistence. Brain 2000;123 Pt 3:508–18.
[5] Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 1995;80: 695–705.
[6] Hemmer B, Vergelli M, Gran B, Ling N, Conlon P, Pinilla C, et al. Predictable TCR antigen recognition based on peptide scans leads to the identification of agonist ligands with no sequence homology. J Immunol 1998;160:3631–6.
[7] Cohen IR. The cognitive paradigm and the immunological homunculus. Immunol Today 1992;13:490–4.
[8] Ben Nun A, Wekerle H, Cohen IR. Vaccination against autoimmune encephalomyelitis with T-lymphocyte line cells reactive against myelin basic protein. Nature 1981;292:60–1.
[9] Lider O, Reshef T, Beraud E, Ben Nun A, Cohen IR. Anti-idiotypic network induced by T cell vaccination against experimental autoimmune encephalomyelitis. Science 1988;239: 181–3.
[10] Lohse AW, Mor F, Karin N, Cohen IR. Control of experimental autoimmune encephalomyelitis by T cells responding to activated T cells. Science 1989;244:820–2.
[11] Medaer R, Stinissen P, Truyen L, Raus J, Zhang J. Depletion of myelin-basic-protein autoreactive T cells by T-cell vaccination: pilot trial in multiple sclerosis. Lancet 1995;346:807–8.
[12] Stinissen P, Zhang J, Medaer R, Vandevyver C, Raus J. Vaccination with autoreactive T cell clones in multiple sclerosis: overview of immunological and clinical data. J Neurosci Res 1996;45:500–11.
[13] Zhang J, Medaer R, Stinissen P, Hafler D, Raus J. MHC-restricted depletion of human myelin basic protein-reactive T cells by T cell vaccination. Science 1993;261:1451–4.
[14] Zhang J, Vandevyver C, Stinissen P, Raus J. In vivo clonotypic regulation of human myelin basic protein-reactive T cells by T cell vaccination. J Immunol 1995;155:5868–77.
[15] Hermans G, Medaer R, Raus J, Stinissen P. Myelin reactive T cells after T cell vaccination in multiple sclerosis: cytokine profile and depletion by additional immunizations. J Neuroimmunol 2000;102:79–84.
[16] Hermans G, Denzer U, Lohse A, Raus J, Stinissen P. Cellular and humoral immune responses against autoreactive t cells in multiple sclerosis patients after T cell vaccination. J Autoimmun 1999;13:233–46.
[17] Zhang JZ, Rivera VM, Tejada-Simon MV, Yang D, Hong J, Li S, et al. T cell vaccination in multiple sclerosis: results of a preliminary study. J Neurol 2002;249:212–8.
[18] Correale J, Lund B, McMillan M, Ko DY, McCarthy K, Weiner LP. T cell vaccination in secondary progressive multiple sclerosis. J Neuroimmunol 2000;107:130–9.
[19] Elias D, Reshef T, Birk OS, Van Der ZR, Walker MD, Cohen IR. Vaccination against autoimmune mouse diabetes with a T-cell epitope of the human 65-kDa heat shock protein. Proc Natl Acad Sci USA 1991;88:3088–91.

[20] Holoshitz J, Naparstek Y, Ben Nun A, Cohen IR. Lines of T lymphocytes induce or vaccinate against autoimmune arthritis. Science 1983;219:56–8.
[21] Kakimoto K, Katsuki M, Hirofuji T, Iwata H, Koga T. Isolation of T cell line capable of protecting mice against collagen-induced arthritis. J Immunol 1988;140:78–83.
[22] Beraud E, Kotake S, Caspi RR, Oddo SM, Chan CC, Gery I, et al. Control of experimental autoimmune uveoretinitis by low dose T cell vaccination. Cell Immunol 1992;140:112–22.
[23] Shapira OM, Mor E, Reshef T, Pfeffermann RA, Cohen IR. Prolongation of survival of rat cardiac allografts by T cell vaccination. J Clin Invest 1993;91:388–90.
[24] van Laar JM, Miltenburg AM, Verdonk MJ, Leow A, Elferink BG, Daha MR, et al. Effects of inoculation with attenuated autologous T cells in patients with rheumatoid arthritis. J Autoimmun 1993;6:159–67.
[25] Atlan H, Gersten MJ, Salk PL, Salk J. Can AIDS be prevented by T-cell vaccination?Immunol Today 1993;14:200–2.
[26] Agnholt J, Kaltoft K, Jakobsen NO, Dahlerup JF. T-cell vaccination in Crohn's disease: principles and presentation of the first two cases. Cytokines Cell Mol Ther 2002;7:117–23.
[27] Zhang J, Markovic-Plese S, Lacet B, Raus J, Weiner HL, Hafler DA. Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. J Exp Med 1994;179:973–84.
[28] Van der Aa A, Hellings N, Medaer R, Gelin G, Palmers Y, Raus J, et al. T cell vaccination in multiple sclerosis patients with autologous CSF-derived activated T cells: results from a pilot study. Clin Exp Immunol 2003;131:155–68.
[29] Zang YC, Hong J, Tejada-Simon MV, Li S, Rivera VM, Killian JM, et al. Th2 immune regulation induced by T cell vaccination in patients with multiple sclerosis. Eur J Immunol 2000;30:908–13.
[30] Cohen IR. The life and times of T cell vaccination. In: Zhang J, Raus J, editors. T cell vaccination and autoimmune disease30. Georgetown, Texas: R.G. Landes Co, 1995.
[31] Herkel J, Brunner S, Meyer zum Buschenfelde KH, Lohse AW. Humoral mechanisms in T cell vaccination: induction and functional characterization of anti-lymphocytic autoantibodies. J Autoimmun 1997;10:137–46.
[32] Zang YC, Hong J, Rivera VM, Killian J, Zhang JZ. Preferential recognition of TCR hypervariable regions by human anti-idiotypic T cells induced by T cell vaccination. J Immunol 2000;164:4011–7 (In Process Citation).
[33] Vandenbark AA, Hashim G, Offner H. Immunization with a synthetic T-cell receptor V-region peptide protects against experimental autoimmune encephalomyelitis. Nature 1989;341:541–4.
[34] Vandenbark AA, Chou YK, Whitham R, Mass M, Buenafe A, Liefeld D, et al. Treatment of multiple sclerosis with T-cell receptor peptides: results of a double-blind pilot trial. Nat Med 1996;2:1109–15 (see comments:published erratum appears in Nat Med Feb 1997;3(2):240).
[35] Minami Y, Weissman AM, Samelson LE, Klausner RD. Building a multichain receptor: synthesis, degradation, and assembly of the T-cell antigen receptor. Proc Natl Acad Sci USA 1987;84:2688–92.
[36] Broeren CP, Lucassen MA, van Stipdonk MJ, Van Der Zee R, Boog CJ, Kusters JG, et al. CDR1 T-cell receptor beta-chain peptide induces major histocompatibility complex class II-restricted T–T cell interactions. Proc Natl Acad Sci USA 1994;91:5997–6001.
[37] Pamer E, Cresswell P. Mechanisms of MHC class I—restricted antigen processing. Annu Rev Immunol 1998;16:323–58.
[38] Mor F, Reizis B, Cohen IR, Steinman L. IL-2 and TNF receptors as targets of regulatory T–T interactions: isolation and characterization of cytokine receptor-reactive T cell lines in the Lewis rat. J Immunol 1996;157:4855–61.
[39] Correale J, Rojany M, Weiner LP. Human $CD8^+$ TCR-alpha beta(+) and TCR-gamma delta(+) cells modulate autologous autoreactive neuroantigen-specific $CD4^+$ T-cells by different mechanisms. J Neuroimmunol 1997;80:47–64.
[40] Hong J, Zang YC, Tejada-Simon MV, Li S, Rivera VM, Killian J, et al. Reactivity and regulatory properties of human anti-idiotypic antibodies induced by T cell vaccination. J Immunol 2000;165:6858–64.
[41] Stinissen P, Zhang J, Vandevyver C, Hermans G, Raus J. Gamma delta T cell responses to activated T cells in multiple sclerosis patients induced by T cell vaccination. J Neuroimmunol 1998;87:94–104.
[42] Shevach EM. Regulatory T cells in autoimmmunity*. Annu Rev Immunol 2000;18:423–49.
[43] Chatenoud L. Do NKT cells control autoimmunity?J Clin Invest 2002;110:747–8.
[44] Hafler DA, Cohen I, Benjamin DS, Weiner HL. T cell vaccination in multiple sclerosis: a preliminary report. Clin Immunol Immunopathol 1992;62:307–13.

The World of Autoimmunity; Literature Synopsis

Nasal instillation of myelin basic protein in experimental autoimmune encephalomyelitis

Whereas mucosal treatment with antigens tend to down-regulate disease, Melo et al. (J Autoimmun 2004;22:13) report exacerbation of murine experimental autoimmune encephalomyelitis (EAE) following nasal instillation of guinea pig myelin basic protein (MBP). There was a tendency towards exacerbation of subsequent disease in animals if they were nasally exposed to MBP during the neonatal period, compared to later exposure during adulthood. However, at 11 months of age this tendency to exacerbate disease course-disappeared. It is unknown whether such exposure early in life has similar consequences in humans.